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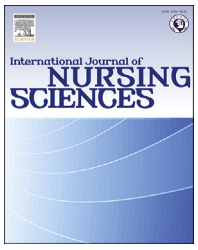

Original Article

The effect of subcutaneous injection duration on patients receiving low-molecular-weight heparin: Evidence from a systematic review

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ABSTRACT

To assess the effect of the injection duration of subcutaneous low-molecular-weight heparin (LMWH) on pain and bruising in patients. Randomized controlled trials and quasi-experimental studies were searched for in four electronic databases. The pooled effect size was expressed as relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI) for dichotomous and continuous data. Cochrane Q and p value were used to assess heterogeneity and the I^2 statistic was adopted to quantify the level. Finally, eight studies involving a total of 532 participants met our inclusion criteria. The slow (30 second) injection was associated with a reduction in pain intensity and duration, and lower bruising occurrence at 48–72 hours and 48 hours post injection. The bruising area was also smaller at 48 hours and 60 hours post injection. No differences were identified between the slow and fast (10 second) injection in bruising area and bruising occurrence at 24 hours and 60 hours post injection. With present evidences, slow injection of LMWH is beneficial to the patient's well being, but further studies to identify the feasibility and standardization of the technique is recommended.

1. Introduction

Pharmaceutical administration is an extremely important component of daily nursing service and extensively applied in emergency and rehabilitation settings. Some medicines, especially those administrated via subcutaneous (SC), intradermal or intramuscular, put extra responsibilities on nurses to explore safe and standard injection techniques to minimize unnecessary pain and potential complications [1,2].

Abbreviations: SC, subcutaneous; LWMH, low-molecular-weight-heparin; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; JBI-MASTARI, Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument; RR, relative risk; MD, mean difference; RCTs, randomized controlled trials.

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As a type of heparin, low molecular weight heparin (LMWH) is only administered subcutaneously [3]. LMWH is frequently prescribed for preventing or treating venous thromboembolism because of its high bio-availability and predictable anticoagulant effect [4,5]. However, just like any other drugs, the use of LMWH does not come without possible adverse reactions. SC heparin preparations often cause adverse effects (AEs) such as bruising, pain, induration and hematoma at the injection site [6,7]. In this regard, previous study has indicated that these local complications increased the patients physical and psychological discomfort and thus resulted in patients' distrust in nurses' efficiency [8,9]. In addition, the bruising can also restrict the possible area for future SC injection and reduce the opportunities for site rotation [10,11].

Literature related to the SC heparin injection have explored the potential factors which might minimize those side reactions and considered that the selection of syringe size and injection site, the application of ice and aspiration, and the injection duration can impact the occurrence of bruising and pain [12–15]. Among them, injection duration is an important influence factor. The researchers recommended giving SC LMWH injections over a 10-s duration [11,12], but which injection duration technique is ideal is far from clear.

Several Studies [16,17] previously have investigated the effects of injection duration on adverse outcomes at the injection site associated with SC administration of LMWH. Although exhaustive association trials have been undertaken to settle this issue, it hasn't yet been obtained a definitive conclusion, and those results haven't been recur. To provide more information for nursing practice, this systematic review examines existing knowledge to objectively assess the influence of two different injection techniques (10-s versus 30-s) on pain and bruising at the injection site in hospitalized patients who require LMWH therapy.

2. Material and methods

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement [18] and Cochrane Handbook for Systematic Reviews of Interventions were adopted to guide the systematic review and meta-analysis [19]. All pooled analyses were grounded on previously published literature, and thus no ethical approval and patient informed consent were required.

2.1. Inclusion and exclusion criteria

We pre-specified the inclusion criteria for our study according to the PICOS format (which describes the participants, intervention, comparison, outcomes and study design). The details of this criterion were as following: (1) **P**: participants were considered meet the inclusion criteria if they were (a) 18 years or older; (b) administered LMWH therapy subcutaneously in hospital. (2) ***I*** and **C**: Two techniques of 30-s SC administration of LMWH in the one site of the abdomen as the intervention and 10-s SC administration of LMWH in the other site of the abdomen as the control were performed. (3) **O**: the pain intensity, the incidence of bruising and the size of bruising at the injection site were listed to be as primary outcome of measures and bruising dimensions and the site-pain duration were viewed as secondary outcomes. (4) **S**: Randomized controlled trials (RCTs) and quasi-experimental methodology would be appraised and included in the review.

It was ineligible for the study if the patients were currently on any other anticoagulant therapy. Study without a comparison group were excluded. Language of publication was imposed into English or Chinese through August, 2015.

2.2. Search strategies

We searched PubMed, EMBASE, the Cochrane Library, and the China National Knowledge Infrastructure (CNKI) to collect potential relevant randomized controlled trials (RCTs) and quasi-experimental studies through August, 2015. The search strategies utilized are shown in Appendix A. Next, the reference lists of included articles were manually searched to include any eligible studies.

2.3. Data abstraction

Two investigators (L-JY and TS) independently extracted the following basic information and essential continuous and binary data for expected outcome of interest from each included study using the predesigned data extraction form (Table 1): study ID which included first author and publication year, country, number of participants, demographics of subjects (age and gender), intervention, reported outcome of interest. The author would be contacted to acquire the complete data when necessary. If researchers provided inconsistent data for same outcome, we would obtain the most rational one. Any divergences between authors concerning the eligibility of a study were resolved by consulting a third author until a consensus was obtained (XT).

2.4. Quality appraisal

Risk of bias was assessed for RCTs using the Cochrane Risk of Bias Assessment tool (19) and for quasi-experimental study using the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MASTARI) (see Appendix B) independently by two investigators (ZZ and LM). Disagreement was resolved by consulting a third investigator (G-MS). The Cochrane Risk of Bias Assessment tool addresses six specific domains as follows: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. The risk of each included study was rated as 'low bias risk', 'unclear bias risk' or 'high bias risk' in accordance with the adequate degree of information extracted. The JBI-MASTARI tool based upon a quantity of critical questions fastened on the aspects of study design that research has shown to affect significantly the validity, for example, randomization, allocation, blinding and reporting. Each study was thus evaluated for quality utilizing the below checklist.

Table 1 – Characteristics of included trials

Author (publication year)	Country	Target disease	Injection protocol	Age (E/C)	Sex (male/female)	Interventions		Outcome
						Slow injection group (E)	Fast injection group (C)	
Zaybak A (2006)	Turkey	Cardiovascular disease, fractures, stroke	Insertion angle 90°; injection without drug aspiration; interval: 12h;	55.52 ± 12.37	25/25	Heparin was injected over 30 seconds on the left or right side of the abdomen	Heparin was injected over 10 seconds on the other side of the abdomen	a + b + c + e + f
Sendir M (2015)	Turkey	Total hip arthroplasty, total knee arthroplasty	Insertion angle 90°; injection without drug aspiration; interval: 24h;	62.7 ± 8.83/57.9 ± 12.5	E: 7/13 C: 6/14	Heparin was injected over 30 seconds on the one side of the abdomen	Heparin was injected over 10 seconds on the other side of the abdomen	a + b + d
Dehghani K (2014)	Iran	Acute coronary syndrome	Insertion angle 90°; injection with drug aspiration; interval: 12h; drug dose: 60–80 mg Enoxaparin	35–75	36/34	Heparin was injected over 30 seconds on the left or right side of the abdomen	Heparin was injected over 10 seconds on the other side of the abdomen	c + e
Dadaeen A (2015)	Iran	Cardiology, neurology, orthopedic	Insertion angle 90°; 27 gage needle; injection without drug aspiration; interval: 12/24 h; drug dose: 40 mg with volume of 0.4 mL or 60 mg with volume of 0.6 mL Enoxaparin; air lock: 0.2 mL inserted	47.78 ± 20.19	70/30	Heparin was injected over 30 seconds on the right side of the abdomen	Heparin was injected over 10 seconds on the left side of the abdomen	a + c + e
Palese A (2013)	Italy	Unclear	Insertion angle 90°; 27.5 gage needle; syringe volume (0.4 mL); injection with drug aspiration; interval: 24h; drug dose: 4000 IU/0.4 mL Enoxaparin	74.8 ± 15.5	48/102	Heparin was injected over 30 seconds on the right side of the abdomen	Heparin was injected over 10 seconds on the left side of the abdomen	b + d
Deng QX (2009)	China	Myocardial infarction, deep venous thrombosis, cerebral thrombosis angina	Insertion angle 90°; interval: 12 drug dose: 0.4 mL LMWH	57.6 ± 9.6	29/23	Heparin was injected over 30 seconds on the left side of the abdomen	Heparin was injected over 10 seconds on the right side of the abdomen	a + b + c
Balci AR (2008)	Turkey	Chronic obstructive lung disease	Insertion angle 90°; 27 gage needle; injection without drug aspiration; interval: 24 h; drug dose: 4500 IU/0.45 mL Tinzaparin; air lock: 0.2 mL inserted	60.02 ± 11.77	23/13	The second morning heparin was injected over 10 seconds on the left abdominal site	The first morning heparin was injected over 10 seconds on the right abdominal site	b + d + e
Chan H (2001)	Australia	Stroke	Insertion angle 90°; 27.5 gage needle; syringe volume (0.5 mL); injection without drug aspiration; interval: 12 h; drug dose: 5000 IU/0.2 mL Dalteparin; use air lock	40–85	20/14	Heparin was injected over 30 seconds on the left or right side of the abdomen	Heparin was injected over 10 seconds on the other side of the abdomen	a + b + c + d + e

a = pain intensity; b = incidence of bruising; c = size of bruising; d = bruising dimensions; e = range of bruising size; f = pain duration.

2.5. Statistical analyses

The pain intensity and pain duration, the incidence, size and dimension of bruising at the injection site were calculated. Heterogeneity was evaluated using the Chi^2, corresponding P value. The level of heterogeneity was quantified by using I^2 statistic. If I^2 was ≥50%, the eligible study was considered to be heterogeneity and a random-effects model was conducted. In contrary, a fixed-effect model was performed. The pooled effect size was expressed as relative risk (RR) and mean difference (MD) with 95% confidence intervals (CI) for dichotomous and continuous data, respectively. A two-side P value of 0.05 indicates statistical significance. The descriptive analysis was adopted to objectively present the results across eligible study in terms of outcomes of interest which were ineligible for quantitative analysis. Considering different types of studies exist different risk of bias and measures of effect, We attempted to combine evidence respectively for RCTs and quasi-experimental studies. All pooled analyses were performed using Review Manager (RevMan) 5.3.0 (the Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Search outcome

The search initially yielded 952 records. After screening title, abstract and full-text, a total of 8 studies were eligible for inclusion in the review. Among these trials, 5 were RCTs [2,4,8,20,21] and three were quasi-experimental non-randomized studies [7,9,22] (see Fig. 1). The full texts of these articles were obtained for analysis.

3.2. Characteristics of included trials

Seven articles [2,4,7–9,20,21] were published in English and one [22] in Chinese, and a total of 532 participants were included. The characteristics of 8 publications were abstracted and assessed (see Table 1).

3.3. Assessment of risk of bias

We presented an assessment of the methodological quality using Cochrane Collaboration's tool for the five RCTs (see Table 2). Additionally, we critically applied the JBI-MAStARI tool for appraising the quality of incorporated quasi-experimental studies (see Table 3). Risk of bias for the five RCTs was discussed under the subheadings below.

3.3.1. Random sequence generation

Most randomized clinical trials lacked the description of the randomization process. All studies appeared to be randomized, but there was only one studies [2] for which the method of sequence generation could be confirmed in sufficient detail to ascertain true randomization. So only one study was judged to be at low risk of bias and four studies at unclear risk of bias for this domain.

3.3.2. Allocation concealment

Only one study [21] was deemed to report allocation concealment adequately, so it is judged as being at low for risk of bias. For the rest of studies, method not stated, so they are judged at unclear risk of bias in this domain.

3.3.3. Blinding

Most of included studies [4,8,20,21] used a design with the subjects as their own control. It was hard to envisage how blinding of subjects could be applicable, because every participant had both slow and fast injections techniques, during the period of the study, participants would know which programs not be experienced. Because evaluation of the pain intensity mainly depended on the subjective judgment of participants, it could influence the outcomes in a large extent for whether implement blinding for participants. Meanwhile, it was also impossible to blind the personnel owing to the nature of intervention. Furthermore, only blinding of outcome assessment could be completed in these trials, two studies [4,21] not reported assessor blinding for pain evaluation, and one study [8] not reported assessor blinding for bruising measurement, according to the outcomes they reported, the domain of two articles were regarded as “unclear risk” and one as “low risk”. Other two studies [2,20] stated all injections and post-injection measurements were conducted by same researcher for both group, which produced high performance and detection bias. They were regarded as “high risk” in this domain.

3.3.4. Incomplete outcome data

There was no drop-outs or losses to follow up. Therefore, they were considered to be at low risk of attrition bias for this domain.

3.3.5. Selective report

All trials adequately reported all expected measure outcomes of interest in the paper and were deemed to be at low risk of bias.

3.3.6. Other potential source of bias

All studies were funded by non-commercial organizations. However, the description about other aspects of heparin injection was scarce, such as amount of heparin, syringe size, needle gage and injection volume. These factors may have an potential effect to the outcomes. To assess potential publication bias, we planned to perform a funnel plot and assess it asymmetry visually, however, only five studies included in this meta-analysis, it was not appropriate owing to lack of detecting power.

3.4. Intervention effects

3.4.1. Pain intensity

A total of 5 reports [2,4,7,8,22] including 3 RCTs and 2 quasi-experimental trials investigated the site-pain intensity. Pain assessment was performed immediately after each injection. Among them, Dadaeen et al. [4] applied Wilcoxon non-parametric test to compare pain severity between the two

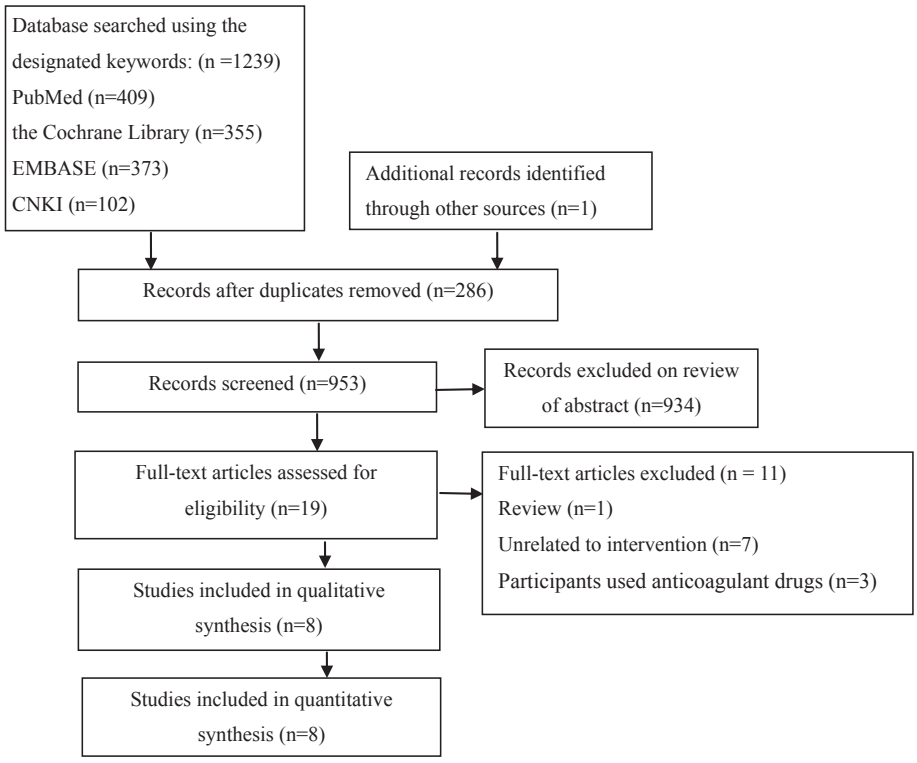

Fig. 1 – PRISMA flow diagram of retrieval and selection of literature.

Table 2 – Risk of bias in randomized control trials

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Dadaeen A (2015)	U	U	H	U	L	L	U
Dehghani K (2014)	U	U	H	H	L	L	U
Palese A (2013)	U	L	L	L	L	L	U
Sendir M (2015)	L	U	H	U	L	H	U
Zaybak A (2006)	U	U	H	U	L	L	U

Q1 = random sequence; Q2 = allocation concealment; Q3 = blinding of participants and personnel; Q4 = blinding of outcome assessment; Q5 = incomplete outcome data; Q6 = selective reporting; Q7 = other bias; H = high bias; L = low bias; U = unclear bias.

interventions, so we only made a qualitative analysis. Two RCTs [2,8] and two quasi-experimental studies [7,22] were quantitatively synthesized with clinical and statistical homogeneity in the pain intensity, respectively. (RCTs: P = 0.34, I^2 = 0%; quasi-experimental studies: P = 0.49, I^2 = 0%), and thus a fixed-effect model of analysis were used. The treatment effects significantly differed between the two groups (RCTs: MD = −3.05, 95% CI: −5.02, −1.08, P = 0.002; quasi-experimental studies: MD = −8.73, 95% CI: −11.23, −6.24, P < 0.000) (Fig. 2A, B). Moreover, Dadaeen et al. (4) used the Numeric Rating Scale to measure pain intensity, and the results showed the median and interquartile range of pain intensity scores in 10- and 30-s injection were 5 (4–7) and 3 (1.25–5), respectively, (p < 0.001).

3.4.2. *Incidence of bruising*

Six studies [2,7–9,21,22] which included 3 RCTs and 3 quasi-experimental studies employed the incidence of bruising as outcome. No overall heterogeneity for polled existed in both types of studies (RCTs: P = 0.48, I^2 = 0%; quasi-experimental studies: P = 0.65, I^2 = 0%). On completion of the intervention period, the slow injection reduced the risk of occurring a bruising by 43% and 40%, severally. Subgroup analysis which was conducted on the basis of evaluating time demonstrated that the 30-s injection was more effective than 10-s injection in reducing the bruising occurrence (48–72 hours – RCTs: RR = 0.63, 95% CI: 0.46, 0.87, P = 0.006; 48 hours-RCTs: RR = 0.53, 95% CI: 0.36, 0.77, P = 0.00; 48 hours-quasi-experimental studies: RR = 0.60, 95% CI: 0.45, 0.81, P = 0.00; 48–72 hours-quasi-experimental studies: RR = 0.63, 95% CI: 0.42, 0.94, P = 0.02) except in 60 hours after injection (quasi-experimental studies: RR = 0.56, 95% CI: 0.30, 1.02, P = 0.06) (Fig. 3A, B).

Table 3 – Risk of bias in quasi-experimental studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Deng QX (2009)	NA	NA	U	Y	U	Y	Y	Y	Y	Y
Balci AR (2008)	NA	NA	U	Y	Y	Y	Y	Y	Y	Y
Chan H (2001)	NA	NA	U	Y	U	Y	Y	Y	Y	Y

Y = Yes; N = No; U = Unclear; NA = Not Applicable; See Appendix B for question list.

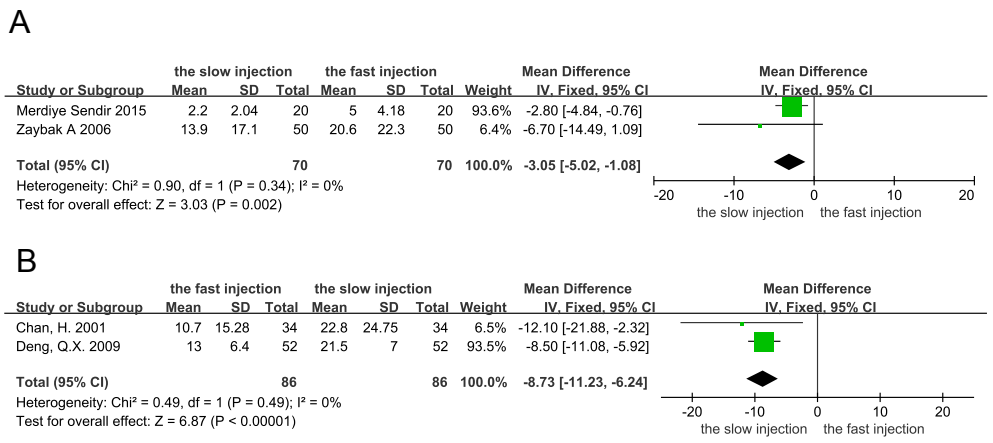

Fig. 2 – A) Meta-analyses for pain intensity (RCTs). Meta-analysis fixed-effects estimates were used. B) Meta-analyses for pain intensity (quasi-experimental studies). Meta-analysis fixed-effects estimates were used.

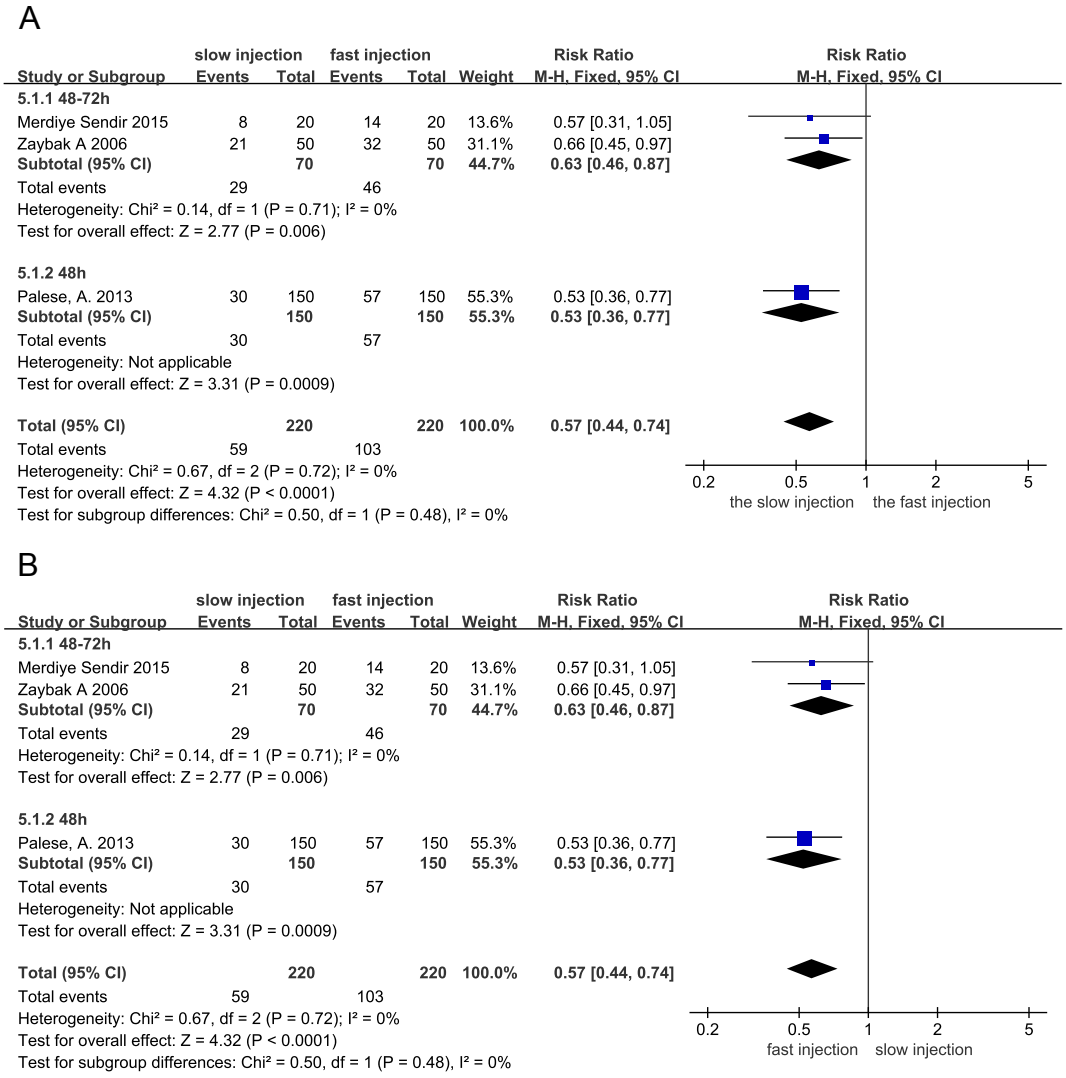

Fig. 3 – A) Meta-analysis for incidence of bruising (RCTs). Meta-analysis fixed-effects estimates were used. B) Meta-analysis for incidence of bruising (quasi-experimental studies). Meta-analysis fixed-effects estimates were used.

3.4.3. *Bruising area*

A total of 6 articles [2,4,7,8,20,22] which divided into 4 RCTs and 2 quasi-experimental studies reported the bruising area. The bruising area was marked on a transparent measuring paper or talc and calculated in mm^2. Among them, Sendir et al. [2] used a completely different method to measure the surface area of bruise tracings, this heterogeneity might reduce the comparability of the available results, and thus we only made a description for it.

Sub-group analysis was conducted due to the different follow-up. For three RCTs [4,8,20], pooled result revealed slow injection has smaller size of bruises compared with fast injection at 48h follow-up (48 hours: MD = −21.79, 95% CI: −23.77, −19.82, P < 0.000). However, no difference was identified between the two techniques at both 24 and 72 hours follow-up (24 hours: MD = 18.71, 95% CI: −18.67, 56.09, P = 0.33; 72 hours: MD = −88.40, 95% CI: −22.16, 44.36, P = 0.19) (Fig. 4). Sendir et al. [2] concluded that an SC injection duration of 30 seconds can result in significantly smaller bruises at 48, 60 and 72 hours after injection. For two quasi-experimental studies [7,22], considering the different injection protocols (drugs, doses and intervals) adopted, we only made a narrative analysis. Chan et al. [7] demonstrated that there was significantly difference between two techniques at both 48 hours (Z = −4.542, P = 0.000) and 60 hours (Z = −4.569, P = 0.000) after each injection. The obtained results conducted by Deng et al. [22] showed the bruise was of bigger size in fast injection technique compare to slow injection technique at both 48 hours (P = 0.008) and 72 hours (P = 0.016) post injection. The conflicting conclusions is likely, whereas, to ascribable to the inappropriate timing of bruise data collection. According to the evidence available, the bruising usually peaks at 48 hours and tends to resolution around 72 hours after the use of LMWH [23,24].

3.4.4. *Bruising dimension*

One RCT [21] and one quasi-experimental study [9] were involved in this indicator. As the difference of studies types exist, we only made a descriptive analysis. Balci et al. [9] considered the slow injection has larger bruises than the fast injection at 48 hours after injection (P = 0.000), but Palese et al. [21] found no difference in average bruising dimension between treatments at the same time (P = 0.661). This inconsistency caused by the various measurement methods was used to measure diameter extension. The former measured the maximum dimensions only when the shape is irregular, however, the latter recorded the maximum dimension of the bruise whether the shape is regular or not.

3.4.5. *Pain duration*

One RCT [8] and one quasi-experimental study [22] employed the pain duration as outcomes. To determine this outcome, the patients were asked to state the start and end values of their pain. As studies types differ, we only made a qualitative analysis. Both studies demonstrated pain period was shortened following the 30-s injections compared with 10-s injections (P = 0.000 and P = 0.030, respectively).

4. Discuss

4.1. *Necessity*

The SC administration of the anticoagulant LMWH is a regularly performed nursing intervention. Since LWMH inhibit blood coagulation and needle punctures injury the skin tissue [1,25], thus it tends to cause bruising and pain at the injection site. Epidemiology indicates the incidence levels of local bruising vary considerably, range from 20.6% to 88.9% after LMWH administration [7,9]. With a view to easing the pain and improving patients' satisfaction, it is incumbent upon health care professional to investigate the most appropriate SC administration technique of LMWH by manipulated controlling factors. From the physiological perspective, administrating an injection slowly can reduce pain and bruising caused by increased tissue pressure trauma [26]. However, the application of the injection duration not yet formed unified regulations so far.

4.2. *Summary of main results*

Take into account a short of data from only RCTs; we widened our inclusion criteria from RCTs and quasi-experimental studies to make an attempt to increase the number of

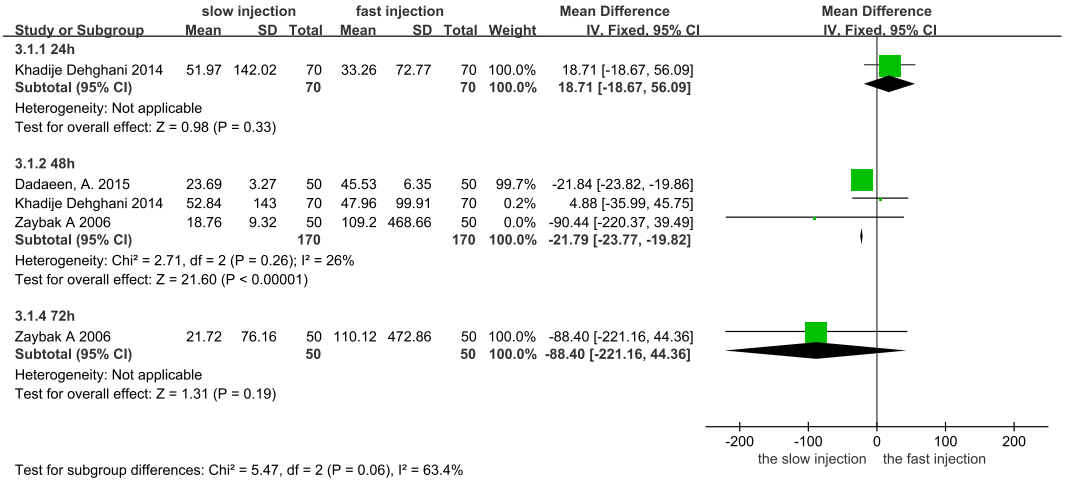

Fig. 4 – Meta-analysis for bruising area (RCTs). Meta-analysis fixed-effects estimates were used.

available information. Eventually, Five RCTs and three quasi-experimental studies met our inclusion criteria. This meta-analysis found evidence that the slow injection technique could effectively improve pain intensity and pain period measured over time and decrease bruising occurrence at both 48–72 and 48 hours follow-up and the bruising size at both 48 and 60 hours follow-up compare to the fast injection technique. But no difference was identified in bruising area and bruising occurrence between groups measured at 24 and 60 hours follow-up. Furthermore, due to insufficient data, we cannot draw a reliable conclusion of whether the slow injection technique can reduce the bruising area at 72 hours follow-up and bruising dimension at 48 hours follow-up.

4.3. *Mechanism*

Possible explanations that why slow injection technique may be effective in pain and bruising are explored: a) SC administration delivers the LMWH into the interstitial space of the hypodermis which contains few arterioles and venues, and thus unabsorbed drugs concentrated the injection site [27]. Slow injection can accelerating drug absorption, reducing tissue stimulation and damage at the injection site [28,29]; b) A fast injection technique cause tissue damage due to the rising strength giving to the tissue, while slow injection allow more time for the SC tissue to accommodate the drug, lowering the tissue pressure in the puncture site, and thus result in less nerve fiber endings and tissue injury from mechanical trauma [15,30].

4.4. *Limitation*

We performed this systematic review to generate more accurate results based on enlarged the cumulative sample size, several limitations were need to be acknowledged. Firstly, incomplete search and the restriction of the language can reduce power of pooled results. Secondly, the subjects of included studies suffered different diseases would limit the generalization of evidence. It should be considered adjust the injection period appropriately to accommodate different groups. Third, scarce articles provided a detailed description about whether patients were taking the analgesic medications in process of research, it is an undeniable fact that the usage of analgesic medications affected the assessment of the pain. Except that, injection technique for participants should be more standardized and systematic. We discovered from injection protocol that it still not formed a consensus in the selection of gage needle, the application of aspiration and air lock. These factors may impair the heterogeneity among these studies. So we hope researchers do more studies to provide more standardized, scientific and rationalized way for clinical use.

4.5. *Implications for practice and research*

The current research provides a contribution to the precaution of local complications associated with SC administration of LMWH. Though ice application has already been proved effective in reducing site-pain [6,10], however, it requires additional nursing time and effort. Besides, the use of a larger syringe or a higher gage needle can also result in less tissue pressure trauma [12,31], but it is costly and waste limited resources. Comparing these methods above, slow injection technique may be more practical for nurses.

But there are some issues to think and tackle. Firstly, it is worth considering the feasibility of the technique. Administrating a solution of less than 1 ml in 30 seconds is difficult, especially when assisting confused patients. Other research models that investigate the effect of intermediate injection duration (that is 15 and 20 seconds) for developing new interventions preventing local reactions related to LMWH are strongly recommended. Secondly, the extension of operation time need nurses focus more on keeping warm and protecting privacy of patients. Meanwhile, the studies which use to evaluate the different SC injection sites for LMWH therapy are needed. At present, it is only recommended that injections sites should have a sufficient amount of fat [32], however, whether the abdomen is the only or preferred site for SC injection is still unclear [13,33,34]. Except that, further studies need to pay attention to other outcomes, such as leakage of drugs and hematoma at the injection site. No included studies reported these indicators, but these outcomes have great value for assessing the effect of slow injection and worth to investigate in future studies.

5. Conclusions

Although some limitations may impair the power of this study, we concluded that slow injection can alleviate site-pain, reduce pain time, bruising occurrence and decrease the bruising size as a whole except some slight fluctuations following the measuring time. Thus the clinical practice of utilizing the slow injection as a proper method for SC LMWH injections was supported. In consideration of chance error, more large-scale and design-well prospective studies are warranted to further this conclusion.

Authors' Contributions

L.-J. Yi, X. Tian and T. Shuai conceived the study. L.-J. Yi, X. Tian and T. Shuai collected the data and performed statistical analyses. Z. Zeng helped to collect the data. L.-J. Yi, X. Tian and L. Ma participated in the design, collected the data, and drafted the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare no funding and conflicts of interest. In addition, all authors reviewed the whole manuscript and approved current version to be considered for publication in Research in International Journal of Nursing Sciences®.

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Appendix A

Search strategy via PubMed

Search	Query	Items found
#11	Search #4 AND #7 AND #10	409
#10	Search #8 OR #9	936477
#9	Search random*[Title/Abstract]	787844
#8	Search ("Randomized Controlled Trials as Topic"[Mesh]) OR "Randomized Controlled Trial" [Publication Type]	484103
#7	Search #5 OR #6	13759
#6	Search ((low-molecular-weight heparin[Title/Abstract]) OR low molecular weight heparin[Title/Abstract]) OR LMWH[Title/Abstract]	8902
#5	Search "Heparin, Low-Molecular-Weight"[Mesh]	10264
#4	Search #1 OR #2 OR #3	49379
#3	Search injection duration*[Title/Abstract]	132
#2	Search (subcutaneous injection*[Title/Abstract]) OR SC injection*[Title/Abstract]	17726
#1	Search "Injections, Subcutaneous"[Mesh]	35400

Appendix B

JBI MASTARI Appraisal Tool for Experimental Studies

Reviewer_____ Date _____

Author_____ Year_____ Record Number_____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?				
2. Were participants blinded to treatment allocation?				
3. Was allocation to treatment groups concealed from the allocator?				
4. Were the outcomes of people who withdrew described and included in the analysis?				
5. Were those assessing the outcomes blind to the treatment allocation?				
6. Were control and treatment groups comparable at entry?				
7. Were groups treated identically other than for the named interventions?				
8. Were outcomes measured in the same way for all groups?				
9. Were outcomes measured in a reliable way?				
10. Was appropriate statistical analysis used?				

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (including reasons for exclusion): _____

REFERENCES

[1] Hunter J. Subcutaneous injection technique. Nurs Stand 2008;22(21):41–4.
[2] Sendir M, Büyükyilmaz F, Çelik Z, Tasköprü I. Comparison of 3 methods to prevent pain and bruising after subcutaneous heparin administration. Clin Nurse Spec 2015;29(3):174–80.
[3] Hodgson BB, Kizior RJ. Saunders nursing drug Handbook 2014. Elsevier Health Sciences; 2013.
[4] Dadaeen A, Bahreini M, Bazi P, Ostovar A, Raeisi A, Dobaradaran S. The effect of duration of subcutaneous injection on the extent of bruising and pain intensity at injection sites among patients receiving enoxaparin sodium: a randomized self-controlled clinical trial. Int Cardivascular Res J 2015;9(2):77–82.
[5] Eikelboom JW, Hankey GJ. Low molecular weight heparins and heparinoids. Med J Aust 2002;177(7):379–84.
[6] Kuzu N, Ucar H. The effect of cold on the occurrence of bruising, haematoma and pain at the injection site in subcutaneous low molecular weight heparin. Int J Nurs Stud 2001;38(1):51–9.
[7] Chan H. Effects of injection duration on site-pain intensity and bruising associated with subcutaneous heparin. J Adv Nurs 2001;35(6):882–92.
[8] Zaybak A, Khorshid L. A study on the effect of the duration of subcutaneous heparin injection on bruising and pain. J Clin Nurs 2008;17(3):378–85.
[9] Akpinar RB, Celebioglu A. Effect of injection duration on bruising associated with subcutaneous heparin: a quasi-experimental within-subject design. Int J Nurs Stud 2008;45(6):812–7.
[10] Batra G. Application of ice cube prior to subcutaneous injection of heparin in pain perception and ecchymosis of patients with cardiovascular problems. Nurs J India 2013;105(4):155–9.
[11] Klingman L. Effects of changing needles prior to administering heparin subcutaneously. Heart & Lung J Acute Crit Care 2000;29(1):70–5.
[12] Hadley S, Chang M, Rogers K. Effect of syringe size on bruising following subcutaneous heparin injection. Int J Trauma Nurs 1996;2(4):119–20.
[13] Pourghaznein T, Azimi AV, Jafarabadi MA. The effect of injection duration and injection site on pain and bruising of subcutaneous injection of heparin. J Clin Nurs 2014;23(7–8):1105–13.
[14] Avşar G, Kaşikçi M. Assessment of four different methods in subcutaneous heparin applications with regard to causing bruise and pain. Int J Nurs Pract 2013;19(4):402–8.
[15] Nair P, Kaur S, Sharma YP. Effect of time taken in injecting subcutaneous heparin injection with reference to site pain and bruising among patients receiving heparin therapy. Nurs Midwifery Res 2008;4(1):7–15.
[16] Babaie Asl F, Kheradmand M, Jafarian R. Effect of duration of subcutaneous heparin injection on its subsequent pain. KAUMS J (FEYZ) 2008;12(2):34–8.
[17] Chenicek TE. Effects of injection duration on site-pain intensity and bruising associated with subcutaneous administration of Lovenox (enoxaparin sodium). 2004.
[18] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336–41.
[19] Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions version 5.1. 0. 2011. The Cochrane Collaboration; 2011 [updated March 2011]. Available from: www cochrane-handbook org.
[20] Dehghani K, Najari Z, Dehghani H. Effect of subcutaneous enoxaparin injection duration on bruising size in acute coronary syndrome patients. Iran J Nurs Midwifery Res 2014;19(6):564.
[21] Palese A, Aidone E, Dante A, Pea F. Occurrence and extent of Bruising according to duration of administration of subcutaneous Low-Molecular-Weight Heparin: a quasi-experimental case-crossover study. J Cardiovasc Nurs 2013;28(5):473–82.
[22] Deng Q, Li R, Li X. Effect of subcutaneou slow-molecular-weight heparin injection duration on bruize and pain. West China Med J 2009;24(2):300–2.
[23] Vanbree NS, Hollerbach AD, Brooks GP. Clinical evaluation of three techniques for administering low-dose heparin. Nurs Res 1984;33(1):15–9.
[24] Wooldridge J, Jackson J. Evaluation of bruises and areas of induration after two techniques of subcutaneous heparin injection. Heart & lung J Crit care 1988;17(5):476–82.
[25] Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the seventh ACCP conference on antithrombotic and thrombolytic therapy. CHEST J 2004;126(3 suppl):188S–203S.
[26] Beyea SC, Nicoll LH. Subcutaneous administration of heparin: an integrative review of the research. Worldviews Evidence-based Nurs presents archives Online J Knowl Synthesis Nurs 1996;3(1):1–5.
[27] Richter WF, Bhansali SG, Morris ME. Mechanistic determinants of biotherapeutics absorption following SC administration. AAPS J 2012;14(3):559–70.
[28] McCONNELL EA. Administering subcutaneous heparin. Nursing2014 2000;30(6):17.
[29] Yevzlin AS, Sanchez RJ, Hiatt JG, Washington MH, Wakeen M, Hofmann RM, et al. Concentrated heparin lock is associated with major bleeding complications after tunneled hemodialysis catheter placement[C]//Seminars in dialysis. Blackwell Publ Ltd 2007;20(4):351–4.
[30] Guyton A, Hall J. Textbook of medical physiology. 11th. 2006.
[31] Arendt-Nielsen L, Egekvist H, Bjerring P. Pain following controlled cutaneous insertion of needles with different diameters. Somatosens Mot Res 2006;23(1–2):37–43.
[32] Annersten M, Willman A. Performing subcutaneous injections: a literature review. Worldviews Evidence-Based Nurs 2005;2(3):122–30.
[33] Fahs PSS, Kinney MR. The abdomen, thigh, and arm as sites for subcutaneous sodium heparin injections. Nurs Res 1991;40(4):204–7.
[34] Owens DR, Coates PA, Luzio SD, Tinbergen JP, Kurzhals R. Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. Diabetes Care 2000;23(6):813–9.